Weekly *nab*-Paclitaxel in Combination With Carboplatin as First-Line Therapy in Patients With Advanced Non–Small-Cell Lung Cancer: Analysis of Safety and Efficacy in Patients With Diabetes

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Abstract

The association between diabetes and clinical outcomes in patients with advanced non–small-cell lung cancer (NSCLC) is unclear. Therapy with *nab*-paclitaxel plus carboplatin (*nab*-P/C) improved the primary end point (overall response rate) versus solvent-based paclitaxel plus carboplatin (sb-P/C) in the overall population and in a subset of patients with diabetes in a phase 3 trial of advanced NSCLC. Rate of neuropathy was lower with *nab*-P/C versus sb-P/C. *nab*-P/C is preferable for patients with NSCLC and diabetes.

Purpose: To examine outcomes in a phase 3 trial of *nab*-paclitaxel plus carboplatin (*nab*-P/C) versus solvent-based paclitaxel plus carboplatin (sb-P/C) in a subset of patients with advanced non–small-cell lung cancer (NSCLC) and diabetes. **Patients and Methods:** Patients with stage IIIB/IV NSCLC received *nab*-P 100 mg/m^2 on days 1, 8, and 15 or sb-P 200 mg/m^2 on day 1, both with C at an area under the curve of 6 mg·min/mL on day 1 every 3 weeks. Overall response rate (ORR) and progression-free survival (PFS) were determined by blinded, independent, centralized review. *P* values were based on chi-square test for ORR and log-rank test for overall survival (OS) and PFS. **Results:** Of the 1052 randomized patients in the phase 3 trial, 61 had diabetes according to prespecified terms (*nab*-P/C, 31; sb-P/C, 30). ORR for *nab*-P/C versus sb-P/C in this subset was 52% versus 27% (relative risk ratio, 1.935; $P = .046$), median PFS was 10.9 versus 4.9 months (hazard ratio, 0.420; $P = .016$), and median OS was 17.5 versus 11.1 months (hazard ratio, 0.550; $P = .057$). Treatment differences in PFS remained significant ($P \leq .036$) after adjusting for histology, region, stage, race, and age and also remained significant in OS for histology ($P = .039$). Patients with diabetes experienced lower rates of grade 3 or higher neutropenia and peripheral neuropathy and higher rates of thrombocytopenia and anemia with *nab*-P/C versus sb-P/C. **Conclusion:** *nab*-P/C demonstrated improved efficacy and manageable tolerability in patients with advanced NSCLC and diabetes.

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Introduction

Diabetes is a serious and growing health problem.[1,2] An estimated 387 million people had diabetes worldwide in 2014, and that number is expected to rise beyond 592 million in less than 25 years.[2] The most recent estimates from 2014 indicate that in North America, 39 million people were living with diagnosed diabetes and 10.5 million people were living with undiagnosed diabetes.[2] Although the exact incidence of diabetes in patients with advanced non–small-lung cancer (NSCLC) has not been well

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studied, some evidence suggests that patients with diabetes are at an increased risk of developing certain cancers.[3]

There are many issues plaguing patients with diabetes and cancer that can affect treatment outcomes and tolerability.[4,5] For example, diabetes is often accompanied by several complications, including diabetic neuropathy, which is estimated to develop in up to 50% of patients.[6] Because peripheral neuropathy is also an adverse effect of many chemotherapeutics, patients with diabetes and cancer could be prone to this reaction more so than patients with cancer without diabetes.[7] Taxanes, a class of chemotherapeutics associated with dose-limiting peripheral neuropathy, are commonly used to treat advanced NSCLC.[7-10] Additionally, steroids are particularly problematic for patients with diabetes because these compounds affect glucose metabolism and are often implicated as a cause of hyperglycemia.[11-13] Steroids may also be associated with the development of diabetes.[14] Many solvent-based chemotherapy agents such as paclitaxel and docetaxel require steroid premedication.[10,15] Furthermore, patients with diabetes may also receive suboptimal therapy due to an increased number of dose reductions or less aggressive treatment.[16,17]

While some evidence has suggested that diabetes is associated with increased survival in lung cancer, several studies have shown the opposite.[18-22] A retrospective study evaluated the prognostic value of several clinical characteristics of 442 patients with advanced NSCLC receiving first-line, platinum-based doublet chemotherapy and concluded that the presence of diabetes at baseline was a significant negative prognostic factor for both progression-free survival (PFS) and overall survival (OS).[23] On the basis of these and other previously published data, improved treatment options for patients with diabetes and advanced NSCLC may be needed.[18-21,23]

nab-paclitaxel in combination with carboplatin (*nab*-P/C) is approved for the first-line treatment of locally advanced or metastatic NSCLC in patients who are not candidates for curative surgery or radiation therapy.[9] In a large, multicenter phase 3 trial, first-line *nab*-P/C significantly improved the primary end point (overall response rate [ORR]) over solvent-based paclitaxel plus carboplatin (sb-P/C; 33% vs. 25%; response rate ratio [RRR], 1.313; 95% confidence interval [CI], 1.082-1.593; $P = .005$), with a trend toward improved OS and PFS.[24] *nab*-P/C was associated with significantly lower rates of grade 3 or higher neuropathy, neutropenia, arthralgia, and myalgia but a higher incidence of thrombocytopenia and anemia compared with sb-P/C.

Compared with the solvent-based formulation of paclitaxel, *nab*-paclitaxel has demonstrated several distinct pharmacokinetic/pharmacodynamic advantages, including higher mean maximum serum concentration of free paclitaxel, higher paclitaxel concentration delivery to tumors (preclinical xenograft models), as well as enhanced transport across endothelial cell monolayers.[25,26] In addition, a recent population pharmacokinetic/pharmacodynamic study demonstrated that *nab*-paclitaxel was associated with a faster and deeper tissue penetration and slower elimination of paclitaxel compared with the solvent-based formulation in patients with advanced solid tumors.[27] Furthermore, in contrast to solvent-based paclitaxel, steroid premedication is not required prior to *nab*-paclitaxel administration because this formulation does not require the use of a solvent.[9,10]

The current analysis examined outcomes with *nab*-P/C versus sb-P/C in a subset of patients with advanced NSCLC and diabetes enrolled onto this phase 3 trial.

Patients and Methods

The patients, study design, and methods were previously reported.[24] Briefly, chemotherapy-naive patients with histologically or cytologically confirmed stage IIIB (with or without pleural effusion) or stage IV NSCLC, measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.0, were eligible for this study. An Eastern Cooperative Oncology Group performance status of 0 to 1 and a life expectancy of $>$ 12 weeks were required. Patients were randomly assigned (1:1) to receive either a 30-minute infusion of *nab*-P 100 mg/m^2 on days 1, 8, and 15 followed by C at an area under the curve (AUC) of 6 mg•min/mL (per Calvert formula) provided on day 1 every 21 days or a 3-hour infusion of sb-P 200 mg/m^2 plus C AUC 6, both provided on day 1 every 3 weeks. Stratification factors in the phase 3 trial included stage (IIIB vs. IV), age ($<$ 70 vs. $\geq$ 70 years), sex, region (North America vs. Australia/New Zealand vs. Eastern Europe vs. Asia/Pacific), and histology (squamous vs. adenocarcinoma vs. other). At least 6 cycles of treatment were encouraged, and patients could continue on treatment in the absence of disease progression or unacceptable toxicity at the investigator's discretion. Tumors were assessed every 6 weeks during treatment by spiral computed tomography scans and until tumor progression after treatment. All patients who received $\geq$ 1 dose of study drug were included in the safety evaluation.

The primary end point of the phase 3 trial was ORR (complete and partial response) by independent radiologic review according to RECIST. Secondary end points included PFS by independent review, OS (follow-up for 18 months after treatment), and safety. All randomized patients were evaluated for efficacy (intent-to-treat [ITT] population).

Identification of Patients With Diabetes

This analysis evaluated the efficacy and safety of *nab*-P/C and sb-P/C in patients with and without diabetes enrolled onto this phase 3 trial. Patients with diabetes were identified based on the pretreatment signs and symptoms reported by investigators. Terms used to identify patients with diabetes were diabetes mellitus, glucose tolerance impaired, pancreatogenous diabetes, and type 2 diabetes mellitus.

Statistical Methods

The percentage of patients with ORR (95% CI) was summarized for patients with and without diabetes. *P* values for ORR were based on the chi-square test, and those for OS and PFS were based on the log-rank test. Stratification (region and histology) was applied in testing the treatment difference for the nondiabetic population, but not for the diabetic population due to the small sample size. Adverse events (AEs) were summarized by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0. PFS and OS treatment comparisons were verified by adding a baseline characteristic to the log-rank test as a stratification factor. Region (North America/Australia, Eastern Europe, or Asia/Pacific), histology (squamous or nonsquamous), current stage of cancer (IIIB or IV), race (white or Asian/African heritage/other),

Table 1 Baseline Characteristics of Patients With and Without Diabetes

Characteristic	Patients With Diabetes		Patients Without Diabetes	
	nab-P/C (n = 31)	sb-P/C (n = 30)	*nab*-P/C (n = 490)	sb-P/C (n = 501)
Age, median (range), years	65 (50-81)	65 (49-78)	59 (28-80)	60 (24-84)
Male sex, n (%)	26 (84)	20 (67)	366 (75)	377 (75)
Median weight, kg	75	77	69	70
Median BMI, kg/m^2	26.4	26.64	23.99	23.89
Race, n (%)				
Asian	10 (32)	8 (27)	69 (14)	72 (14)
African heritage	1 (3)	1 (3)	11 (2)	7 (1)
White	18 (58)	20 (67)	398 (81)	413 (82)
Hispanic/Latino	2 (6)	0	9 (2)	5 (1)
Other	0	1 (3)	3 (1)	4 (1)
ECOG PS, n (%)				
0	7 (23)	6 (20)	126 (26)	107 (21)
1	24 (77)	24 (80)	361 (74)	392 (78)
2	0	0	3 (1)	2 (< 1)
Histology, n (%)				
Adenocarcinoma	21 (68)	14 (47)	233 (48)	250 (50)
Squamous cell	9 (29)	8 (27)	220 (45)	213 (43)
Carcinoma not otherwise specified	1 (3)	6 (20)	28 (6)	27 (5)
Large cell	0	2 (7)	9 (2)	11 (2)
Stage at Randomization, n (%)				
IIIB	6 (19)	3 (10)	102 (21)	107 (21)
IV	25 (81)	27 (90)	388 (79)	394 (79)
Smoking Status, n (%)				
Never smoked	6 (19)	8 (27)	131 (27)	136 (27)
Smoked and quit	21 (68)	19 (63)	147 (30)	129 (26)
Still smokes	4 (13)	3 (10)	210 (43)	231 (47)
Country, n (%)				
Australia	0	2 (7)	5 (1)	7 (1)
Canada	1 (3)	3 (10)	20 (4)	20 (4)
Japan	9 (29)	4 (13)	65 (13)	71 (14)
Russia	9 (29)	12 (40)	229 (47)	219 (44)
Ukraine	1 (3)	1 (3)	119 (24)	134 (27)
United States	11 (35)	8 (27)	52 (11)	50 (10)
Metformin therapy, n (%)	10 (32)	11 (37)	NA	NA
Peripheral Neuropathy, Grade at Baseline, n (%)				
0	22 (73)	25 (86)	475 (97)	477 (95)
1	8 (27)	4 (14)	14 (3)	23 (5)
2	0	0	1 (< 1)	0

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; NA = not applicable; *nab*-p/c = *nab*-paclitaxel plus carboplatin; PS = performance status; sb-P/C = solvent-based paclitaxel plus carboplatin.

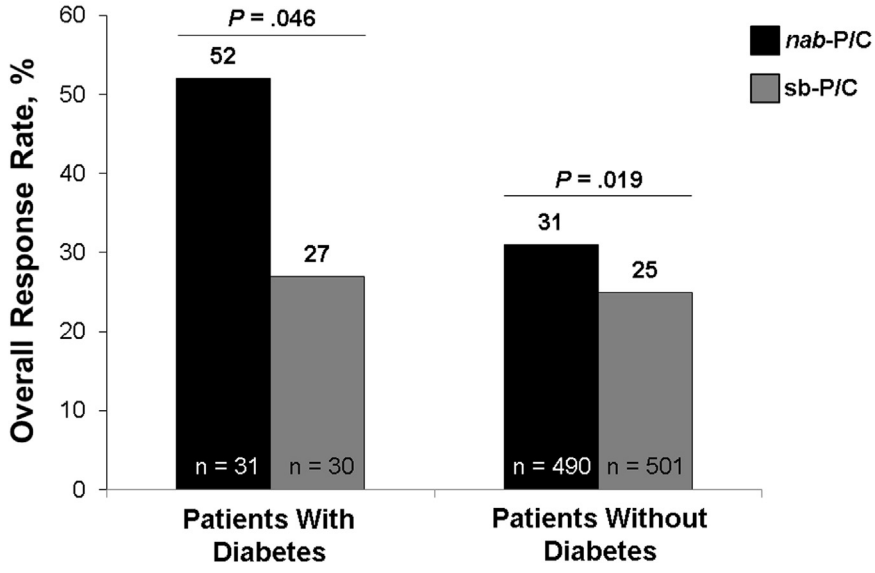
and age (< 70 or ≥ 70 years) were added to the stratified log-rank test one at a time in the sensitivity analysis.

Results

Of the 1052 randomized patients in the study population, 61 were considered to have diabetes according to the prespecified terms (*nab*-P/C, 31; sb-P/C, 30; Table 1) and 991 did not have diabetes (*nab*-P/C, 490; sb-P/C, 501). Similar to the ITT population, baseline characteristics were generally well balanced between the treatment arms in patients without diabetes. Some exceptions in patients with diabetes were noted. Among patients with diabetes, a higher percentage of patients treated with *nab*-P/C were men, had adenocarcinoma, and were from Japan, while a higher percentage of patients treated with sb-P/C had carcinoma not otherwise specified and were from Russia. In addition, baseline characteristics were comparable between patients with diabetes versus those without

Figure 1 Independent Radiologic Assessment of Overall Response in Patients With and Without Diabetes. [a]The 95% CIs for Response Rate Ratios (RRRs) Were Calculated According to Asymptomatic 95% CI of Relative Risk of *nab*-Paclitaxel Plus Carboplatin (*nab*-P/C) Versus Solvent-Based Paclitaxel Plus Carboplatin (sb-P/C)

	With Diabetes	Without Diabetes
RRR[a]	1.935	1.270
95% CI	0.976-3.837	1.039-1.553
P value	**.046**	**.019**



diabetes, regardless of treatment. A higher percentage of patients with diabetes than those without diabetes previously smoked and quit, were of Asian origin, were from the United States, and had adenocarcinoma, while a higher percentage of patients without diabetes than those with diabetes were white, had squamous histology, currently smoked, and were from the Ukraine. Among patients with diabetes, 10 (32%) and 11 (37%) in the *nab*-P/C and sb-P/C arms received concomitant metformin therapy, respectively. Most patients with or without diabetes had grade 0 peripheral neuropathy at baseline. However, a higher percentage of patients with diabetes in the *nab*-P/C versus sb-P/C arm had grade 1 peripheral neuropathy at baseline.

Efficacy Results

In patients with diabetes, the ORR was significantly higher with *nab*-P/C versus sb-P/C (52% vs. 27%; RRR, 1.935; 95% CI, 0.976-3.837; $P = .046$; Figure 1). *nab*-P/C treatment also resulted in a significantly longer median PFS compared with sb-P/C in these patients (10.9 vs. 4.9 months; hazard ratio [HR], 0.42; 95% CI, 0.200-0.868; $P = .016$; Figure 2A). The median OS was longer in patients with diabetes receiving *nab*-P/C versus sb-P/C (17.5 vs. 11.1 months; HR, 0.55; 95% CI, 0.298-1.026; $P = .057$; Figure 2B), but statistical significance was not reached. In patients without diabetes, *nab*-P/C treatment also resulted in a significant improvement in ORR versus sb-P/C (31% vs. 25%; RRR, 1.270; 95% CI, 1.039-1.553; $P = .019$; Figure 1). In addition, the median PFS with *nab*-P/C and sb-P/C in these patients was 6.0 and 5.8 months (HR, 0.95; 95% CI, 0.801-1.116; $P = .515$), respectively, and the median OS with *nab*-P/C and sb-P/C was 11.6 and 11.2 months (HR, 0.95; 95% CI, 0.817-1.101; $P = .489$), respectively.

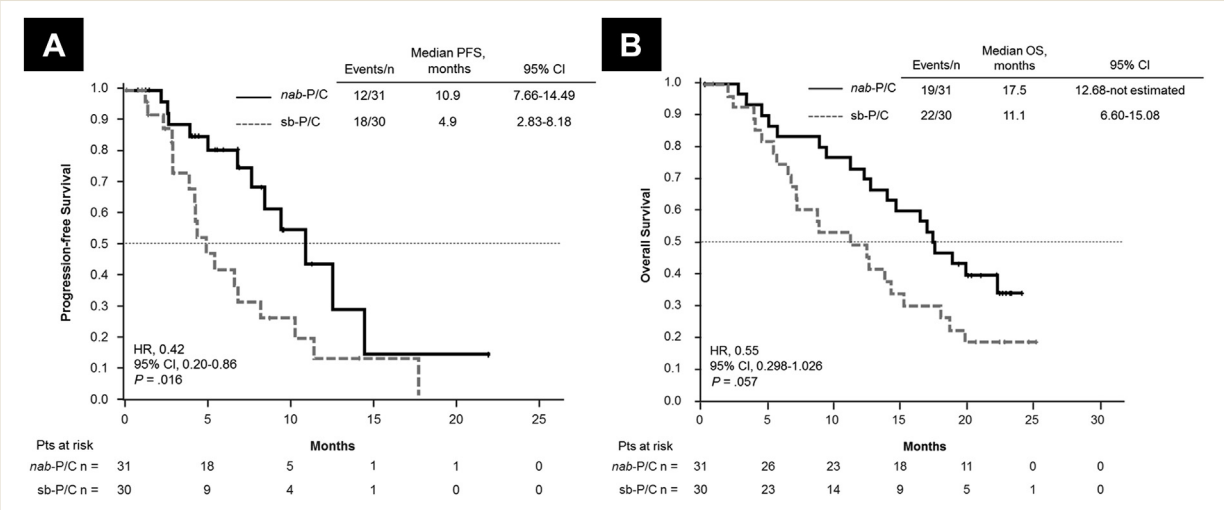
Sensitivity Analysis

In patients with diabetes, the treatment effect on PFS remained significant for *nab*-P/C after being adjusted for histology, region, stage, race, and age ($P \leq .036$; Table 2). For OS, the treatment difference between *nab*-P/C and sb-P/C in patients with diabetes was significant only when stratifying by histology ($P = .039$).

Treatment Effects and Exposure

Taxane dose intensity, cumulative dose, and frequency of dose reductions were higher with *nab*-P/C versus sb-P/C in patients with and without diabetes (Table 3). The median number of cycles was similar in both treatment arms in patients with and without diabetes (Table 3).

Figure 2 Survival in Patients With Diabetes. (A) Kaplan-Meier Curve of Progression-Free Survival (PFS) in Patients With Diabetes. (B) Kaplan-Meier Curve of Overall Survival (OS) in Patients With Diabetes



Abbreviations: HR = hazard ratio; *nab*-P/C = *nab*-paclitaxel plus carboplatin; pts = patients; sb-P/C = solvent-based paclitaxel plus carboplatin.

Safety

Among patients with diabetes, numerically lower rates of grade 3 or higher neutropenia and higher rates of thrombocytopenia and anemia were noted with *nab*-P/C versus sb-P/C (Table 4). With regard to nonhematologic AEs, a lower incidence of grade 3 or higher fatigue, arthralgia, and myalgia but a higher incidence of anorexia was observed with *nab*-P/C versus sb-P/C treatment. Incidence of key AEs in patients without diabetes was comparable to that in patients with diabetes.

In patients with diabetes, grade 3 or higher peripheral neuropathy was higher with sb-P/C versus *nab*-P/C. By NCI CTCAE, grade 3 or higher peripheral neuropathy was 7% with *nab*-P/C versus 20% with sb-P/C. Similarly, peripheral neuropathy by Medical Dictionary for Regulatory Activities was 7% with *nab*-P/C versus 20% with sb-P/C. In patients without diabetes, sb-P/C treatment also resulted in higher incidence of grade 3 or higher peripheral neuropathy compared with *nab*-P/C. Patients with diabetes treated with *nab*-P/C generally experienced a longer time to onset of grade 3 or higher peripheral neuropathy versus those treated with sb-P/C (187 vs. 121 days). In patients without diabetes, time to onset of grade 3 or higher peripheral neuropathy was also longer with *nab*-P/C versus sb-P/C (121 vs. 103 days).

Table 2 Treatment Effects Adjusted by Stratification Factor for Patients With Diabetes

Efficacy End Point	Stratification Factor	HR sb-P/C/*nab*-P/C	*P*[a]
PFS	Region	0.32	.010
	Histology	0.40	.015
	Race	0.45	.036
	Stage	0.44	.026
	Age	0.39	.013
OS	Region	0.54	.055
	Histology	0.52	.039
	Race	0.56	.066
	Stage	0.56	.071
	Age	0.57	.069

Abbreviations: *nab*-P/C = *nab*-paclitaxel plus carboplatin; OS = overall survival; PFS = progression-free survival; sb-P/C = solvent-based paclitaxel plus carboplatin.
[a]Based on stratified log-rank test.

Discussion

This analysis described outcomes of a subset of patients with advanced NSCLC and diabetes enrolled onto a large phase 3 trial.[24] The results of this analysis demonstrated that *nab*-P/C is effective and well tolerated in patients with advanced NSCLC and diabetes. In the current analysis of patients with diabetes, *nab*-P/C resulted in a significantly higher ORR and longer PFS compared with sb-P/C treatment. Treatment differences in PFS remained significant after adjustment for baseline characteristics, including histology, region, stage, race, and age. A greater than 6-month improvement in OS was also observed in the *nab*-P/C arm, but it did not reach statistical significance. In patients without diabetes, *nab*-P/C treatment also resulted in a significant improvement in ORR and nonsignificantly longer survival outcomes compared with sb-P/C.

No new or unexpected safety signals were noted in patients with diabetes compared with the ITT population.[24] In this analysis, a numerically lower rate of grade 3 or higher neutropenia and peripheral neuropathy and a higher rate of thrombocytopenia and anemia were noted with *nab*-P/C versus sb-P/C treatment in patients with and without diabetes. Hematologic events were manageable with dose modifications. The incidence of key AEs in patients with diabetes was comparable with that of patients without diabetes, further supporting the use of this treatment regimen in this select patient population.

Table 3 Treatment Exposure

Parameter	Patients With Diabetes		Patients Without Diabetes	
	nab-P/C (n = 30)	sb-P/C (n = 30)	*nab*-P/C (n = 484)	sb-P/C (n = 494)
Median cycles administered, n (min, max)	6 (1, 24)	5 (1, 25)	6 (1, 31)	6 (1, 30)
Patients who received ≤6 cycles of therapy, n (%)	17 (57)	15 (50)	249 (51)	266 (54)
Median Dose Intensity				
Taxane, mg/m^2/wk	79	66	82	65
Carboplatin, AUC/wk	1.50	1.96	1.50	1.95
Median Cumulative Dose				
Taxane, mg/m^2	1450	900	1313	1150
Carboplatin, AUC	31	27	29	33
Patients With ≥1 Dose Reduction, n (%)				
Taxane	18 (60)	7 (23)	221 (46)	114 (23)
Carboplatin	18 (60)	7 (23)	218 (45)	116 (23)

Abbreviations: AUC = area under the curve; *nab*-P/C = *nab*-paclitaxel plus carboplatin; sb-P/C = solvent-based paclitaxel plus carboplatin.

While the correlation remains inconclusive, studies have demonstrated worse outcomes in patients with cancer and diabetes compared with patients with cancer but without diabetes.[20,22,23] A prospective, single-center study demonstrated that survival was significantly longer ($P = .007$) in patients with locally advanced NSCLC without diabetes (n = 76) versus those with locally advanced NSCLC and diabetes (n = 11).[20] Similarly, in a large retrospective analysis of 442 patients with advanced NSCLC receiving first-line treatment with platinum doublets, diagnosis of diabetes at baseline was associated with a significantly negative prognostic influence on both OS (odds ratio, 2.38; 95% CI, 1.48-3.81; $P < .01$) and PFS (odds ratio, 1.83; 95% CI, 1.20-2.79; $P = .005$).[23] In the current study, outcomes appeared to be better in patients with diabetes treated with *nab*-P/C compared with those in patients without diabetes, although no formal statistical analyses were performed between these groups. This trend was not observed in patients with diabetes treated with sb-P/C.

Patients with diabetes often receive suboptimal treatment, which can affect outcomes. In this study, the median number of *nab*-P/C cycles was 6 in patients with diabetes, which was the same in the ITT population and patients without diabetes.[24] Although a higher percentage of patients with diabetes receiving *nab*-P/C had ≥ 1 dose reduction compared with sb-P/C, dose intensity and cumulative dose were higher with *nab*-P/C treatment, and efficacy outcomes did not appear to be affected. These results indicated that *nab*-P/C may be a suitable treatment for patients with diabetes and advanced NSCLC.

Table 4 Select Grade 3 or Higher Treatment-Related Adverse Events by NCI CTCAE

Adverse Event	Patients With Diabetes		Patients Without Diabetes	
	nab-P/C (n = 30)	sb-P/C (n = 30)	*nab*-P/C (n = 484)	sb-P/C (n = 494)
Hematologic Laboratory Abnormalities, %				
Neutropenia	53	55[a]	47[b]	58[c]
Thrombocytopenia	20	7	18[b]	9[d]
Anemia	23	10	28[b]	7[c]
Nonhematologic Events, %				
Fatigue	7	10	7	9
Peripheral neuropathy	7	20	3	11
Arthralgia	0	3	0	2
Myalgia	0	3	<1	2
Anorexia	3	0	2	1

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; *nab*-P/C = *nab*-paclitaxel plus carboplatin; NCI = National Cancer Institute; sb-P/C = solvent-based paclitaxel plus carboplatin.
[a]n = 29.
[b]n = 478.
[c]n = 484.
[d]n = 483.

Patients with diabetes have various complications, making treatment decisions for patients with cancer and diabetes challenging.[4,5] Chronically high blood glucose levels can injure nerves and cause a range of neuropathic symptoms.[28] Therefore, patients with diabetes may be particularly susceptible to peripheral neuropathy, which could be exacerbated or aggravated by taxane treatment. In this trial, *nab*-P/C treatment was associated with fewer instances of grade 3 or higher peripheral neuropathy compared with sb-P/C, and this result was similar in patients with or without diabetes. A higher percentage of patients with diabetes had grade 1 peripheral neuropathy at baseline in the *nab*-P/C versus sb-P/C arm. Despite this, a lower percentage of patients with diabetes treated with *nab*-P/C developed grade 3 or higher peripheral neuropathy compared with those receiving sb-P/C treatment. In addition, fluctuations in blood glucose are also challenging for patients with diabetes, and steroids are particularly problematic because they can increase blood glucose levels and impact glucose metabolism.[11] Several chemotherapeutic agents (including solvent-based paclitaxel and docetaxel) require steroid premedication to prevent hypersensitivity reactions and therefore may be of limited use in this patient population.[10,15,29,30] In contrast, *nab*-paclitaxel does not require steroid premedication, which makes it a desirable chemotherapeutic option for patients with diabetes.[9]

It is not known why *nab*-P/C was particularly effective in patients with diabetes in the current study. Whether the albumin formulation of *nab*-paclitaxel plays a role in the differences in outcomes between patients with diabetes and those without diabetes is unknown; however, a few studies have provided some high-level evidence of an association. High glucose levels have been shown to increase cultured endothelial cell permeability to albumin in vitro.[31] Similarly, in a rat model of diabetes, hyperglycemia was shown to alter glomerular albumin permeability.[32] Additional studies are required to clarify this issue. Some evidence has suggested that metformin may enhance the effects of treatment in patients with diabetes and various solid tumors, leading to improved outcomes.[33-35] It does not appear that metformin use affected efficacy outcomes in this study, given that more patients with diabetes in the sb-P/C versus *nab*-P/C arm received concomitant metformin (37% vs. 32%). Further studies are required to investigate the relationship between use of metformin and outcomes in patients receiving *nab*-P/C and whether this relationship is associated with the mechanism of action of *nab*-paclitaxel.

While the magnitude of treatment differences between the *nab*-P/C and sb-P/C arms was large for each efficacy end point, sample sizes in this analysis were small, and results should be interpreted in light of this limitation. The sensitivity analysis should also be interpreted with caution because it limited the rigor of the stratified log-rank test. Finally, it is unknown whether chemotherapy schedule, pharmacokinetic profile, steroid use, or other factors contributed to the improved efficacy of *nab*-P/C versus sb-P/C in patients with diabetes in this study.

Patients with cancer and diabetes face a significant treatment challenge, given their predisposition to diabetic neuropathy and the potential exacerbation of this complication by chemotherapeutic drugs. There is a paucity of data from large-scale trials evaluating the impact of diabetes on treatment outcomes in patients with NSCLC. This analysis demonstrated that *nab*-P/C was effective and well tolerated in patients with advanced NSCLC and diabetes and could be a valuable treatment option for this subset of patients with a high unmet need. A prospective, randomized trial of patients with metastatic NSCLC and diabetes treated with *nab*-P/C versus sb-P/C would be important, especially in view of the increasing incidence of obesity and diabetes around the world.

Clinical Practice Points

- The global incidence of diabetes continues to rise. Patients with advanced NSCLC tend to be older; therefore, the risk of diabetes may be higher in these patients. The potential predisposition to chemotherapy-induced peripheral neuropathy makes treatment particularly challenging in diabetic patients. In a phase 3 trial of advanced NSCLC, first-line *nab*-P/C treatment significantly improved the primary end point (ORR) versus sb-P/C. Patients treated with *nab*-P/C experienced significantly less grade 3 or higher neuropathy, neutropenia, arthralgia, and myalgia but more thrombocytopenia and anemia compared with sb-P/C.
- In this retrospective analysis of a subset of patients with diabetes enrolled onto a phase 3 trial, ORR and PFS were significantly improved with *nab*-P/C compared with sb-P/C. Similar to results in the overall population, neutropenia and peripheral neuropathy were lower with *nab*-P/C versus sb-P/C in this patient subset.
- *nab*-P/C appears to be an effective and safe treatment option for patients with diabetes and advanced NSCLC. Given the need for therapeutic options in this patient population, additional study of this treatment combination could be beneficial.

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Disclosure

V.H. is a participant in Celgene advisory boards. A.K., R.P., and M.F.R. are Celgene employees. M.A.S. has stated that he has no conflict of interest.

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